## REMARKS

Claims 1-3, 5-10, and 12-23 are pending in the application. Claims 1-3, 5-10, 12, 13, 15, 16, and 23 were rejected under 35 U.S.C. § 102(b), and claims 14 and 17-22 were rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed as follows.

Rejection under 35 U.S.C. § 102(b)

Claims 1-3, 5-10, 12, 13, 15, 16, and 23 were rejected under 35 U.S.C. § 102(b) as being anticipated by Sauvaire et al., Diabetes 47(2):206-210, 1998. This rejection is based on the Examiner's assertion that Sauvaire teaches that 4-hydroxyisoleucine potentiates insulin secretion, and that administration of 4-hydroxyisoleucine for this purpose would inherently achieve the effects noted by Applicants: induction of insulin sensitization and insulin mimetic effects. Applicants respectfully disagree with this rejection.

First, Applicants note that stimulation of insulin secretion (as taught by Sauvaire) and insulin sensitization (as in the present invention) are two completely different processes, taking place in completely different cell types. Some drugs such as Sulfonylureas possess secretagogue activity (i.e., stimulate insulin secretion), but do not stimulate glucose uptake (i.e., increase insulin sensitization), whereas other drugs such as Metformin can stimulate glucose uptake but have no effect on insulin levels. Other drugs such as GLP-1 analogues have both activities. Thus, as not all drugs acting through one of the two processes described above (insulin secretion and insulin sensitization) necessarily act through the other, it cannot be assumed that a compound such as 4-hydroxyisoleucine, which was known to be capable of stimulating insulin secretion (as shown by Sauvaire), will "automatically" have an insulin sensitizing or insulin mimetic effect, as

in the present invention.

Second, Applicants note that the present claims require that 4-hydroxyisoleucine be administered to patients. In contrast, the teachings of Sauvaire relate only to *in vitro* experiments, in which 4-hydroxyisoleucine is used to treat cultured cells or tissues, and not to administration to patients.

Further, the experiments of Sauvaire employed isolated islets of Langerhans (pancreatic cells), from which insulin secretion was induced. In contrast to stimulating insulin secretion from pancreatic cells, the present invention relates to sensitizing cells that develop insulin resistance. Such an "insulin sensitizing or insulin mimetic effect" can only be observed (a) *in vivo*, and (b) in cells that develop insulin resistance (e.g., muscle cells and fat cells). Such effects cannot be observed in the cells and tissues studied by Sauvaire. Thus, Sauvaire cannot inherently anticipate the presently claimed invention, because under the experimental conditions of Sauvaire (*in vitro*, pancreatic cells) the "insulin sensitizing or insulin mimetic effect" of the present claims simply did not and could not occur.

Finally, Applicants submit that, even if Sauvaire had shown that administration of 4-hydroxyisoleucine to patients stimulates insulin secretion (which it does not), such a teaching would not be an inherent anticipation of the present invention. The methods of the present invention provide treatment options for patients for whom treatment regimens based on the stimulation of insulin secretion would not have been considered. As an example, those skilled in the art, in view of Sauvaire's teaching that 4-hydroxyisoleucine stimulates insulin secretion, would certainly not have considered it helpful to treat patients who produce insulin at or near normal levels, but whose target tissues are not insulin responsive. In contrast, these patients

could be treated according to the present invention, to obtain beneficial effects on their conditions, as the treatment would potentiate the insulin sensitizing and insulin mimetic effects of insulin already produced by the patient. The invention thus provides a novel approach to treating patients with conditions associated with abnormal glucose metabolism, such as diabetes.

Thus, because the Sauvaire reference does not teach the presently claimed invention, either expressly or inherently, Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 14 and 17-22 were rejected under § 103(a) for obviousness over Sauvaire et al., Diabetes 47(2):206-210, 1998, in view of Windholz et al., The Merck Index, 10th edition, 1983, abstract 4866, pp. 723 and 724. This rejection is respectfully traversed.

Claims 14 and 17 specify compositions/kits and methods including both 4-hydroxyisoleucine and insulin. With respect to these claims, the Examiner states that it would have been obvious to administer these agents together, based on Sauvaire's teaching of 4-hydroxyisoleucine as having antidiabetic activity, and Windholz's teaching of insulin as being a well-known antidiabetic agent. The Examiner further states that those skilled in the art would have assumed that combining these agents would lead to an additive effect, in the absence of evidence to the contrary.

Claim 18 specifies oral administration, claims 19 and 20 specify dosing regimens (two or three times per day), and claims 21 and 22 specify particular forms of administration (capsule or

tablet). The Examiner rejects these claims for obviousness, on the basis that variables such as those specified in the claims represent art-recognized approaches to achieving a desired effect.

Applicants first submit that the fact that 4-hydroxyisoleucine and insulin can each be used to treat the same condition does not mean that those of skill in the art would conclude that use of the drugs in combination would lead to an additive effect. If it were possible to generalize in this manner, then that would mean that it would be expected that combining multiple drugs that each have a small effect on a condition would cure the condition, provided that a sufficient number of drugs were included in the combination, and this certainly is not true. Although it is not uncommon for drug combinations to be used in the treatment of certain diseases, including diabetes and related conditions, the finding of an additive effect is simply not predictable, based solely on the premise set forth by the Examiner (i.e., that the drugs are used to treat the same disease). Thus, because there is no suggestion of the claimed combination in the art, and because there would not have been an expectation of an additive effect, as asserted by the Examiner, this rejection should be withdrawn with respect to claims 14 and 17.

With respect to claims 17-22, Applicants note that these claims, in depending from claim 1, require that 4-hydroxyisoleucine be administered to induce "an insulin sensitizing or insulin mimetic effect in a tissue in a patient." In addition to only describing *in vitro* methods, the Sauvaire reference, as discussed above, also only teaches an effect of 4-hydroxyisoleucine on pancreatic islet cells, and not cells or tissues that are affected by the present methods. In particular, the present methods impact cells that are responsive to insulin (e.g., muscle and liver cells), rather than cells that secrete insulin (pancreatic cells). Sauvaire thus provides no suggestion or basis for concluding that 4-hydroxyisoleucine would have any effect on insulin

responsive cells, not to mention the effects noted in the present claims.

Such a teaching is also not provided by the Windholz reference, which, as stated by the Examiner, teaches only that insulin is a well-known agent for use in treating diabetes, and nowhere mentions any effects that 4-hydroxyisoleucine may have. The cited references thus provide no suggestion or motivation to administer 4-hydroxyisoleucine to induce an insulin sensitizing or insulin mimetic effect, whether on its own, in combination with insulin, orally, 2 or 3 times per day, or in a capsule or tablet. The rejection of claims 17-22 under § 103(a) should therefore be withdrawn.

## CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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